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Characteristics of Anaemia Management in Patients with Chronic Kidney Disease

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1. Introduction

Erythrocyte production is narrow regulatory process. Erythropoiesis starts with differentiation of small part of pluripotent stem cells to most primitive erythroid progenitors (Colony Forming Units - CFU and Burst Forming Units – BFU). These progenitors are developing to erythroid precursors, and follow program of specific differentiation to mature erythrocytes. (Suda et al., 1984) Haematopoietic growth factors (interleukin-3, granulocyte-macrophage factor that stimulate colonies and c-kit ligand) are important for the enhancement of progenitor cells, and together with erythropoietin produce large colonies of erythroblasts. (Sieff et al., 1986, 1989) Erythropoietin is crucial for finishing the differentiation of erythroid progenitors. Erythropoietin also has influence on receptors for erythropoietin.
If renal anaemia is not treated there are: cardiac failure, cerebrovascular ishaemic events, lowered cognitive and mental function, tiredness, reactive hypertension, left ventricular hypertrophy, increased morbidity and mortality. (Lau et al., 2010; Marti, 2004; Namiuchi et al., 2005; Streja et al., 2004)

2. Anaemia of chronic kidney disease (CKD) - appearance

Anaemia in CKD in most patients is normochromic and normocytic. It is consequence of lower erythropoietin production because of diminished mass of renal parenchyma and shorter survival of erythrocytes. Anaemia could appear already at creatinine clearance or glomerular filtration rate (GFR) < 35 ml/min/1,73m^2. (Levin, 2007; Locatelli et al., 2008)
In some diseases such as nephronophtysis, medulary cystic disease, endemic or Balkan nephropathy, anaemia can be expressed even at creatinine clearance lower than 60 ml/min/1,73m^2. (Locatelli et al., 2009) Studies in children estimated mean appearance of anaemia in CKD when GFR is lower than 43 ml/min/1,73m^2. (Fadrowski et al., 2008; Yorgin et al., 2001)

2.1 Calculated creatinine clearance from 24 hours urine speciment and estimated GFR (e-GFR)

In children could be used Schwartz (Schwartz-Haycock) formula where from creatinine in serum, height and coefficient according to the age and body mass, could be estimated GFR without 24 hours specimens (Schwartz et al.; 1984, Schwartz & Gauthier, 1985).

$$GFR = k \times (\text{height - cm}/\text{creatinine in serum - } \mu\text{mol/L}) \quad (1)$$

Measured endogenous creatinine values compared with Schwartz formula showed results that anaemia starts at GFR <58 ml/min/1,73m[2]. It is overestimation when using Schwartz´s formula for GFR. (Fadrowski et al., 2008)
In adult patients for estimation of GFR simple Cockcroft-Gault formula is used. Renal function has to be in steady state.

$$GFR=140\text{-age (ys)} \times \text{lean BW(kg)} / \text{creatinine mg/dL} \times 72 \text{ in males} \quad (2)$$

During the last years mostly is used MDRD-GFR formula for patients over 18 years of age that uses creatinine with more precise method than uncompensated kinetic Jaffe´s method. It uses an enzymatic method traceable to the IDMS method and SRM 909b level and is the most preferable formula in adults also in Croatia. (Flegar-Mestric et al., 2010)
The 4-variable equation from the Modificaton of Diet in Renal Disease (MDRD Study) and 6-variable MDRD Study were compared with standardized assay of Cockcroft-Gault equations , and is found better relation to other measurements of GFR. (Cerriotti et al., 2008; Levey et al., 2006)
Values of new enzymatic method of determination of creatinine are investigated also in children and are lower than with Jaffe´s reaction. (Cerriotti et al., 2008) That will bring changes in the estimated value for the patients using Schwartz formula with real (lower) creatinine in serum and may be better determination of estimated GFR, more similar to creatinine clearance in 24 hours urine specimens: MDRD formula can not be used in children and still Schwartz formula is actual.

3. Diagnosis of anaemia

Important is to evaluated mean values of haemoglobin (Hb) and haematocrit (Htc) in normal population according to the age and gender. (Puretic, 2000; Working Party for EBPG, 1999) In children "normal" values according to the age are presented in Table 1.

Age/gender	Hb g/L	Htc %
After birth	165 ± 30	51 ± 9
1 month	140 ± 40	41 ± 6
2-6 months	115 ± 25	35 ± 7
6 mo-2 years	120 ± 15	36 ± 3
2-6 years	125 ± 10	37 ± 3
6-12 years	135 ± 20	40 ± 5
12-18 years/males	145 ± 15	43 ± 6
12-18 years/females	140 ± 20	41 ± 5

Table 1. Mean hemoglobin values (Hb) and haematocrit (Htc) in health population of children (X±SD)

[1] Legend: k (depending on muscular mass): premature children 1st year = 29, newborns 1st year = 40, children and adolescent girls = 48, adolescent boys = 61. Mean in children > 13 years =52
[2] Note: in females GFR is 0,85 of the values in males

Diagnosis and treatment of anaemia should start at values of Hb or Htc < 80% of mean values for the age. (Table 2). (Berns, 2008; Puretic, 2009) At adults evaluation of anaemia is needed at Hb < 11o g/L in females and < 120g/L at males. (Kes & Ljutic, 2008; Locatelli et al., 2004; NKF-K/DOQI, 2006, 2007)
Laboratory diagnostics includes also: Mean Cell (Erythrocyte) Volume - MCV, Mean Content of Haemoglobin in Erythrocytes (Mean Cell Haemoglobin – MCH), Mean Concentration of Haemoglobin in Erythrocytes (Mean Cell Haemoglobin Concentration - MCHC), reticulocyte number, percentage of hypochromic erythrocytes.

Age/gender	Hb g/L	Htc %
After birth	<130	<41
1 month	<110	<33
2-6 months	<90	<28
6 mo-2 years	<95	<29
2-6 years	<100	<30
6-12 years	<110	<32
12-18 years/males	<115	<35
12-18 years/females	<110	<33
Adults/males	<120	<38
Adults/ females	<110	<33

Table 2. Indications for diagnosis and treatment of anaemia (hemoglobin and haematocrit, according to the age, and gender)

Iron parameters are: iron in serum, total iron bound capacity, ferritin and transferrin saturation (TSAT).

$$TSAT\ (\%) = Fe \times 100/TIBC \quad (3)$$

Further investigations are: occult blood in stool, C- reactive protein as marker of chronic inflammation, serum albumin and prealbumin as markers of nutrition.
Additional laboratory and clinical analysis: vitamin B_{12} and folic acid levels in plasma, blood smear, intact parathormon and parameters of haemolysis (haptoglobin, free haemoglobin, methaemalbumin, lactate dehidrogenase, bilirubin, Coomb´s tests, electrophoretic pattern of plasma proteins). (Locatelli et al.; 2009)
In doubt of myelodysplasia bone marrow puncture is needed, and consultation of haematologist. In some cases bone biopsy will confirm secondary hyperparathyreoidismus or bone marrow fibrosis.When mycrocytic anaemia is present, there is probably iron deficiency and not aluminium intoxication, because reverse osmosis in water treatment is used in all dialysis centres , and aluminium based phosphate binders are not more in use. Macrocytosis could be associated with folic acid or vitamin B_{12} deficiency.

4. Goals of anaemia treatment

In anaemia of chronic kidney disease target values for adults are haemoglobin 110-120 g/L. For children recommended are values 80% for age Table 2. (Puretic, 2009)
Values of Hb over 130 mg/L are not recommended because of high risk of heart failure, and cerebrovascular events. (Lau et al., 2010; Streja et al., 2004)

4.1 Significance of iron levels

Before erythropoietin is included in therapy it is important that serum iron is adequate and tissue storages are saturated. Iron therapy has impact on leukocyte surface molecules and reactive oxygen species in haemodialysis patients (Guz et al., 2006)
In the treatment of sideropenia the use of iron sucrose or gluconate and not colloidal forms such as dextrin is recommended. (Chertow et al., 2006) Basic parameters for adequate iron reserves are: ferritin, transferrin saturation and transferrin. Ferritin initially have to be higher than 100 mg/L, TSAT >15% and transferrin in referent values. During maintenance of erythropoietin treatment ferritin should be within range 150-300mg/L (not higher than 400- especially in children and in patients with hepatic lesion). Transferrin saturaton has to be 20-40% and transferrin serum level normal.
At high erythropoietin dosage and ferritin < 100 mg/L) females and diabetics are at higher risk of mortality. (Lau et al., 2010) Iron in patients on haemodialysis is administered intravenously, and in other intravenously or per os, but intravenous iron administration is preferable, also in patients on peritoneal dialysis. (Li & Wang, 2008) In predialysed patients better is also the use of intravenous iron (Hoerl, 2008)
Percentage of hypochromic erythrocytes at start should be usually <10%, and in maintenance phase <5%.

5. Treatment of renal anaemia

Kidney is the primary organ for erythropoietin production, but at adults small quantity is produced also in liver. In the treatment of anaemia androgen drugs are abandoned, and erythrocyte transfusions have "time limited" values, and also have complications (Slonim et al., 2008; Teruya, 2008). The guidelines for assessing appropriateness of pediatric transfusions are introduced (Roseff at al., 2002). The side-effects in potential transmission of viruses are well known. (Pampilon et al., 1998)
Eryhtropoiesis Stimulating Agents (ESA) since 1987 year are present in Croatia. (Gasparovic et al., 1990) Its importance (with the first erythropoietin alfa, and later with erythropoietin beta, darberythropoietin alfa and continuous erythropoietin receptors activation) dominates in the treatment of anaemia in chronic kidney disease and especially in dialysed patients. There are experimental studies that erythropoietin attenuates renal injury in acute kidney injury. (Spandou et al., 2006)
Dosage should be individualised, and careful monitoring of erythrocytes, haemoglobin and haematocrit is necessary so as continuous correction of other possible factors that influence anaemia.
Minimal investigations before starting erythropoietin therapy are: 1) haemoglobin and haematocrit, 2) reticulocytes, 3) mean cell volume (MCV), 4) transferrin saturation (TSAT), 5) serum ferritin and 6) occult blood in stool.

5.1 Indications

Renal anaemia: in dialysed patients and chronic kidney disease in predialysis patients with creatinine clearance < 35 ml/min/1,73m^2 or in selected cases <60 ml/min/1,73m^2. (Locatelli et al., 2009) In children and adults with chronic renal failure of transplanted kidney, and saturated iron reserves, indication is Hb <100 g/L.

5.2 Administration of erythropoietin

Subcutaneous administration of alfa or beta erythropoietin have some advantage over intravenous, because half-life is 24 hours, and intravenously administered 9 hours. (Besarab et al., 2009) In comparison to intravenous administration, during subcutaneous route minimal concentrations remain higher over longer time. That implies that erythropoietin can be administered in longer periods of time if given subcutaneously. (Portoles at al., 2005) Erythropoietin beta could be better metabolically and economically used when applied subcutaneously 3x weekly or 1x weekly, even 1 x in two weeks. (Miroescu et al., 2006) Darberythropoietin alfa is administered once weekly or once in two weeks, even at four weeks. (Carrera et al., 2006; Fang & Chang, 2009) But in patients on haemodialysis erythropoietin is given predominantly intravenously in developed countries, because it has also local side effects as inflammations, haemorrhage or calciphylaxia, and also has historical risk of pure red cell aplasia.

5.3 Initial dosage

Erythropoietin alfa or beta at adults on haemodialysis is administered 1 x 4000 IU/week in slow correction (during 2 - 3 months) or 2 - 3 x 4000 IU/ week in fast correction. Mean dosage is mostly 75-100 IU/kg/week. In peritoneal dialysis doses are lower, because in this patients haemoglobin could be recovered spontaneously during first 3 months. (Puretic, 2000)

There are no exact paediatric data in European or USA guidelines for anaemia management in chronic kidney disease, but are adult data suggested also for children (75-100 IU/kg/week).

In some sporadic reports values for children are higher. In young children: 2 years of age initial dosage is 50 U/kg 3x weekly subcutaneously or rarely intravenous. In older children dosage is 50-150 IU/kg/week or higher.

In children, in randomised double blind trial with placebo control in 222 children aged 5-18 years estimated high dosage in intravenous administration of erythropoietin alfa was 600 IU/kg/week (not to exceed 40,000) and maximal 900 IU/kg/week (not to exceed 60,000U/week). In subcutaneous administration should be used lower dosage. (recommendation of the manufacturer)

With darberythropoietin alfa usual dosage is 0,45 μg/kg BW at adults and children, even at children from age 1 year. (Fang & Chang, 2009; Portoles and al., 2005)

Continuous erythrocyte receptor activator (C.E.R.A.) administration is nowadays used only for patients over 18 years old, but could be used also in postpubertal children. (Carrera et al., 2010)

5.4 Maintenance dosage

Initial dosage after 4 weeks is titrated and changed according to haemoglobin values:

a. Lower dosage for 25% if:
   - target Hb 110-120 is reached

- Hb rises >10 g/L in two weeks

b. Enlarged dosage for 25% if:
   - Hb <100 g/L
   - Hb is not rising for 10 g/L after 4 weeks of therapy

c. not administer erythropoietin for 2-4 weeks if Hb>130 g/L

The mean dosage of erythropoietin alfa or beta in adults on dialysis in maintenance phase is 125 IU/kg/week (range 50-250). In children on chronic haemodialysis mean dosage is 175 IU/kg/week (range 50-450). On peritoneal dialysis the mean dosage is 75 IU/kg /week (range 25-325), in children and adults.

5.5 Novel Erythropoietin Stimulating Agents - ESA´s

Darberythropoietin alfa with different aminoacids structure and more sialyc acid could be administered at longer intervals: 1x weekly or once in 2 weeks, even 1 x per month and is given mostly intravenously 0,45 µg/kg/week. Intravenous half life is 25 hours. Higher sialyc acid content, larger molecular weight and negative charge prolonged its half life 3 times in comparison with erythropoietin alfa and beta. It is usually used once in two weeks. (Carrera et al., 2006; Fang & Chang, 2009)

Last years was developed a novel erythropoietin which is administered once monthly (metoxy poliethylen glycol-erythropoietin beta). It reacts on erythropoietin receptors and acts as continuous erythropoietin receptor activator (C.E.R.A.), and therefore is quite different to other ESA´s.

Initial dosage is 0,6 µg/kg every two weeks, later could be given 1 x monthly intravenously or subcutaneously. (Carrera et al., 2010)

Erythropoietins are today widely used also in patients with chronic renal failure of grade III and IV, and in patients after kidney transplantation with deterioration of graft function, and Hb <100 g/L. The use is justified in adults and in children. Conversion between these drugs is shown in Table 3.

Darberythropoietin alfa (µg) IV or SC dose per week	Erythropoietin alfa or beta (IU) IV or SC dose per week	C.E.R.A. (µg) IV or SC dose per month
<40	<8000	120
40-80	8000-16,000	200
>80	>16,000	360

Table 3. Suggestions for conversion of different erytropoiesis stimulating agents

6. Erythtropoietin in surgical treatment of dialysed patients

If surgical operation is planned in patients with chronic kidney disease erythropoietin could be administered 300 IU/kg 10 days before, than the first and fourth postoperative day to maintain Hb levels 100-130 g/L. (Locatelli et al., 2008)

If patient is on erythropoietin treatment it should not be excluded or diminished. Higher dosage of usual erythropoietin dosage has no approval preoperatively, or first week after operation.

7. Erythropoietin in acute medical disorder of dialysed patients

There are some dilemmas in administration of erythropoietin at acute disorders of organs, so as inflammation, pneumonia, cerebrovascular incident, cardiac failure. There are some opinions to stop the therapy until recovery, but it will lower haemoglobin later, especially in reconvalescent phase, so it has to be maintained at adequate levels of haemoglobin 110-120 g/L.

8. Nutritional status in additional treatment of anaemia

Malnourishment could be expressed in 40-70% in patients on haemodialysis and 30-50% on peritoneal dialysis. Anaemia in this group of patient is more severely expressed weather receive or not iron and erythropoietin therapy. Anamnesis of dietary nutrients, nutritional habits, BMI, exact „dry weight"and anthropometrical measures are important parameters in the overall treatment of anaemia. (Furumatsu et al., 2008)
In children are periodically determined: BW, body hight, head circumference, upper arm circumference, cutaneous fold thickness, development and puberty. It is necessary also to determine plasma proteins: albumin, prealbumin, transferrin, ferritin, aminoacids and cholesterol, urea, creatinine. Ferritin and transferrin are also good parameters of nutrition, and not only of anaemia. (Locatelli et al., 2006)

9. Inadequate response to erythropoietin in anaemia treatment

9.1 Erythropoietin resistance

In patients who are dialysed insufficiently or non-adequately (both, haemodyalised and peritonealy dialysed patients) resistance to erythropoietin occurs. Resistance to erythropoietin treatment is seen also at presence of the chronic inflammatory response on haemodialysis. (Locatelli et al., 2006) The cause could be allergic or toxic reaction to the artificial (bioincompatible) membranes and other plastics, or inadequate water treatment – endotoxins. Also could appear, but rarely in peritoneal dialysis because of plasticizers or endotoxins produced during manufacturing of dialysis solutions - sterile peritonitis. (Geerse et al., 2011) But controversial fact is that erythropoietin therapy acts positively on peritoneal mesangial cells and reducing inflammatory response. (Vorobiev et al., 2008)
The reasons of resistance to erythropoietin could be also subclinical infections, growth hormone deficiency, myelodysplastic syndromes, occult malignomas, HIV infection and haemoglobinopathias. It has to be excluded malnourishment, bone marrow fibrosis and chronic folate and B_{12} deficiency. (Locatelli et al., 2009)

9.2 Pure Red Cell Aplasia mediated with antibodies against erythropoietin

Acquired erythrocite aplasia is very rare disorder of severe anaemia characterized with very low reticulocyte count and practically absence of erythrocite precursors in bone marrow. All

other strains in bone marrow are normal. (Fisch et al., 2000; Howman & Kulkarni,2007) Some cases are idiopathic, in others could be present disorders as: myelodysplastic syndrome, lymphoma, leucemia, autoimmune diseases, thymoma, viral infection (Parvovirus B) or drugs (phenitoin, chloramphenicol).
The incidence of anti erithropoietin antibodies nowadays is signifficantly lower, and sporadic cases are verified also with the use of erythropoietin beta and darberythropoietin. (Bennett et al., 2007)

9.3 Pure red cell aplasia – PRCA - not induced with antibodies against erythropoietin

Numerous reports from 1989- 2004 showed incidence of 1,6/10.000 patients /year with rising to 3,43, mostly with high frequency in patients treated with erythropoietin alfa- administered subcutaneously. In intravenous administration verified were only 2 cases or 0,02/10,000 patients/year which is expected appearance in long term use of human recombinant erythropoietin in population. After change of formulation with change of protection with uncoated rubber stopper syringes, and with change of polysorbate with human plasma albumin frequency is essentially diminished and is as expected in population 0,02/10,000 patients/year. So the reason was of chemical origin. (Boven et al., 2005)

10. Erythropoietin in kidney transplantation

After kidney transplantation anaemia treatment is intriguing and may complicate post transplantation course. Early and late posttransplantation anaemia should be differentiated. (Choukroun & Martinez, 2005)

10.1 Early posttransplant anaemia

Risk factors are: blood loss during or few days after surgery, inflammation, delayed graft function and induction therapy with bone marrow suppression. According to some expert opinions soon after kidney transplantation in selected patients erythropoietin alfa or beta could be used in high dosage up to 125 IU/Kg/every other day IV (up to 400 IU/Kg/week) to partially correct anaemia in the first month after transplantation. (Van Biesen at al., 2005) Rationale was: prevention of blood transfusions and help in wound healing. In the treatment of early anaemia graft function on the other side could be deteriorated. (Gouva et al., 2004) It is contraversary to experimental studies (Spandou et al., 2006) Well known is that in good graft function transplanted kidney starts with own erythropoietin production in 8-30 days, and there is no need for erythropoietin treatment early after transplantation according to controlled studies.

10.2 Late posttransplant anemia

It appears after 1 month of kidney transplantation, and is mostly seen with chronic allograft nephropathy. (Al-Khoury et al., 2006; Baltar et al., 2007) The criteria for the treatment of anaemia are the same as in chronic kidney disease of predialysis patients. (Locatelli et al., 2009) With deterioration of graft function when GFR is lower than 35 ml/min/1,73m^2 and Hb lower than 100 g/L could start anaemia treatment with erythropoietin.

11. Conclusions

Drugs called erythropoiesis stimulating agents are today widely used in patients with chronic renal failure of grade III and IV, patients on haemodialysis or peritoneal dialysis (grade V of chronic renal failure), and in patients after kidney transplantation with deterioration of graft function. Mostly are used in patients with glomerular filtration rate, or creatinine clearance below 35 ml/min/1,73m^{2}. Administration is via intravenous or subcutaneous route. Efficacy of subcutaneous administration could be 20-30% higher, but in hemodialysed patients is justified intravenous administration.

After correction of other causes of anaemia dose of erythropoietin stimulating agents depends on haemoglobin levels, and the time to achieve recommended haemoglobin levels. Their initiation starts when haemoglobin level falls below 8o% of normal values for the age. In children older than 6 years erythropoietin therapy starts at haemoglobin < 100 g/L, or haematocrit < 33%. In adults are introduced when haemoglobin is < 110 g/L, and target haemoglobin is between 110-120 g/L. During maintaining erythropoietin therapy almost always iron supplementation intravenously or peroral is needed.

After kidney transplantation anaemia can occur and may complicate posttransplantation course. According to some opinions soon after kidney transplantation in selected patients erythropoietin alfa or beta could be used in high dosage up to 125 U/Kg/every other day intravenously. According to controlled studies in good graft function grafted kidney starts with own erythropoietin production in 8-30 days and there is no need for erythropoietin treatment.

For late posttransplant anaemia (after 1st month of kidney transplantation) causes are: poor graft function with lack of erythropoietin or erythropoietin resistance, and viral or recurrent bacterial infections. Patients with later poor graft function and chronic anaemia should be treated in the same way as other patients with chronic kidney disease. Introducing erythropoietin therapy according to good clinical practice of haemoglobin levels and to maintain its level as in chronic renal failure before transplantation.

Advantages of the use of erythropoietins are multiple: there is no need for erythrocyte transfusions, and therefore lowered risk for developing of panel reacting antibodies (PRA) or HLA antibodies and transfusion transmitted viruses. Transfusions of blood have to be used only with low leucocytes protocols (e.g. filtered blood) to diminish load of transfusion transmitted viruses (HBV, HCV, CMV, EBV, HIV, TTV) and to lower possible later immunological reaction.

Routine administration of transfusions in patients with chronic kidney diseases is at haemoglobin level < 65-60 g/L, except in surgical needs, or in cardyomyopathic patients.

With recommended haemoglobin levels there is improvement of cardiovascular system, less complications including left ventricular hypertrophy, ischemic heart disease, chronic heart failure, generalised atherosclerosis and stroke. Better is growth and development of child with chronic kidney disease, so as better physical and mental activity and sense of well-being.

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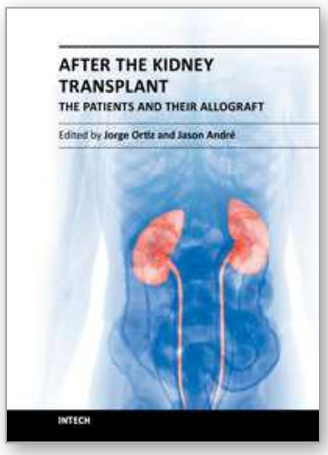

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There are many obstacles in kidney transplantation. For the transplant team, there is the balance between immunosuppression to aid in the recipientâ€™s tolerance of the allograft and the infection risk of a suppressed immune system. These potential long term complications of kidney transplantation are relatively well known, but there are many other complications that patients and families do not consider when preparing themselves for a kidney transplant. Although the benefits of attempting a kidney transplant far outweigh downfalls of the long term sequelae, kidney transplantation is by no means a benign procedure. It is the hope of these authors that the reader will leave with a sense of understanding towards the kidney recipients.

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